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REVIEW ARTICLE

Hypertonic solutions for pediatric patients

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Abstract

Objective: To describe the current knowledge and indications for use of hypertonic saline solutions in pediatrics patients.

Sources of data: Medline recent review articles and personal files.

Summary of the findings: Basic physiologic principles were reviewed concerning the distribution of fluid inside the intravascular, interstitial and intracellular compartments. We also reviewed the findings concerning the mechanisms responsible for the rapid onset of cardiocirculatory effects and the additional effect of the colloid component. Finally, we present the medical terms used in the context of small-volume resuscitation, the indications for clinical use, the evidence from clinical research (hemorrhagic shock, preclinical trauma care, septic shock, and head trauma), and the disadvantages and potential adverse effects of small-volume resuscitation.

Conclusions: Resuscitation by means of hypertonic saline solutions associated or not with colloid solutions is one of the most innovative concepts for primary resuscitation from trauma and shock established in the past decade. Currently, the spectrum of potential indications involves not only prehospital trauma care, but also perioperative and intensive care therapy. However, additional randomized double-blind studies are required with both children and adult patients to confirm the advantages of the method in terms of survival.

J Pediatr (Rio J) 2003;79(Suppl 2):S187-S94: Hypertonic saline, pediatrics, small volume, critical care, fluid resuscitation.

Introduction

It is more than 20 years since the first description was published of research using resuscitation with small volumes of hyperosmotic NaCl solution at 7.5%.[1] Since then, a large mount of work with animals[2-5] and some clinical work with humans[6-9] has been published.

While the concentrations of different particles are different across the different body fluid compartments, osmolality (number of particles per kg of water) is approximately the same (approximately 290 mosm/kg/H_2O) in body fluids (Figure 1). This fact is known as the principle of isoosmolality and is the central principle in understanding water distribution in the body.

Although intracellular and interstitial osmolality are identical, plasma osmolality is slightly higher resulting in important clinical implications for the choice of resuscitation fluid. Plasma has a much higher protein concentration than the interstitial space and these molecules do not pass trough vascular endothelium.

A term that is used to describe a solution is its tonicity which refers to its osmolality relative to plasma. A solution is said to be isotonic when the normal cells of the organism can be suspended in this environment with no

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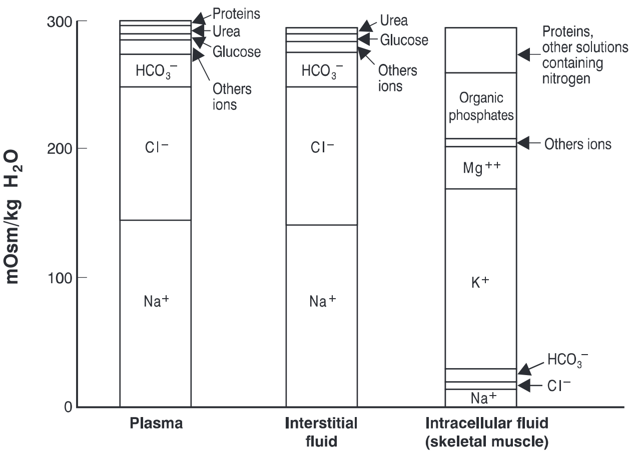

Figure 1 - Plasma osmolar concentration, interstitial and intracellular fluid. Note that the main cation in the plasma and in the interstitial fluid is sodium, while in the intracellular fluid the main cation is potassium. Adaptad from West JBE[10], 1985

alteration in volume. This implies that the solution has the same osmolality as plasma, and they are therefore isoosmolar. Habitually used solutions, such as saline at 0.9% and Ringer lactate are isotonic. The sodium in these solutions will primarily remain within the extracellular space. Therefore, an infusion of saline at 0.9% can result in expansion of the total extracellular space distributed so that 1/3 of the volume is in the intravascular space and 2/3 is in the interstitial space, resulting in no increase to extracellular osmolality nor intracellular volume.

With the use of hypertonic saline solutions, with concentrations of between 3.5% and 7.5%,[11] there is expansion of the extracellular space with temporary hyperosmolality of this compartment relative to the intracellular space. This can result in water being diverted from the intracellular space to the extracellular space with increased intracellular osmolality. The increase in intracellular osmolality and the change in volume can cause significant physiological consequences, irrespective of the increase in hydrostatic pressure resulting from expansion of the intravascular volume.

This therapy is based on instantaneous mobilization of endogenous fluids across an osmotic gradient from the intracellular space to the intravascular compartment. The method becomes attractive because of the rapid mobilization of endogenous water, especially from the intracellular compartment which represents a large fluid reserve (Figure 2).

Additionally during shock and ischemia, there is an increase in endothelial cell volume due to lost adenosine triphosphate (ATP) and cell membrane exchange dysfunction, resulting in water accumulation in the cells. Therefore, any mobilization of water from the intracellular compartment, would have two important advantages: 1) a rapid increase in plasma volume, of 3 to 4 times the infused volume; 2) normalization of endothelial cell volume and luminal diameter recovering small vessels, with increased blood flow in microcirculation as a result (Figure 3).

Medical terms used in small-volume resuscitation

The term small-volume resuscitation was used by Nakayama et al., 1984,[13] in reporting on an experimental model of hemorrhagic shock using sheep, in which there was recovery of cardiac output and a significant increase in systemic pressure immediately after infusion of a hypertonic saline solution (NaCl 7.5% = 2,400 mosm/l). Following this, a number of different clinical and experimental studies were carried out to investigate hypertonic solutions (NaCl, glucose, mannitol, sodium bicarbonate, sodium acetate, saline with lactate, urea, Tris-Cl), with variable doses, (4-6 ml/kg), differing concentrations of sodium chloride (1.5-30% NaCl), speed of infusion (2-15 minutes) and different administration routes (intravenous, intraosseous). This research also evaluated efficacy in respect of restoration of macro and microcirculatory parameters, organ dysfunction and survival rates.

Researchers were concerned about the resuscitation response soon after small-volume resuscitation, when a hypertonic saline solution is used in isolation, therefore the saline solution (7.2-7.5%) was combined with a colloid solution which has an elevated capacity to bond with water (dextran 60/70 4.2-24% or hydroxyethyl starch 60-20%), in order to preserve intravascular volume, thus obtaining a synergic effect from the increase in

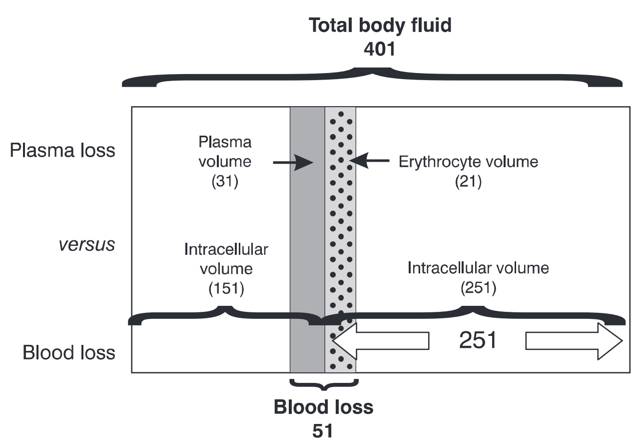

Figure 2 - Body fluids, causes of hypovolemia and the impact of the infusion of hypertonic saline solution in the mobilization of the intravascular compartment. Adaptad from Guyton AC, 1991[12]

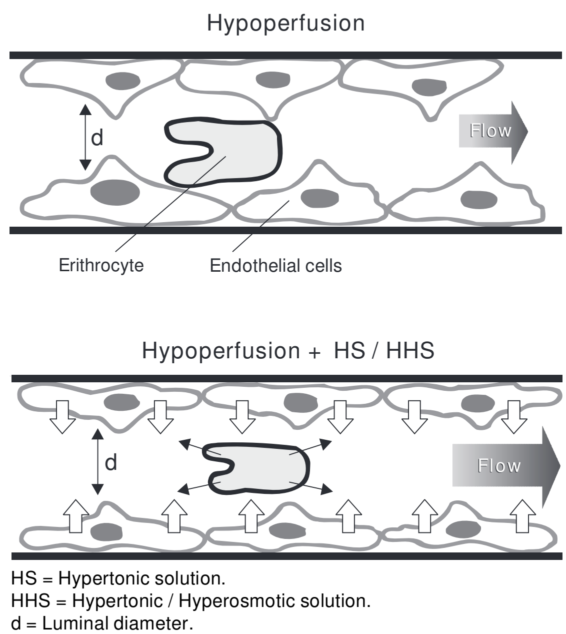

Figure 3 - Microcirculatory effects of hyperosmotic/ hyperoncotic solutions

plasma osmolality with resultant mobilization of intracellular water and increase in plasma oncotic pressure in an attempt to conserve the volume effect.[15] Consequentially, the meaning of small-volume resuscitation or hypertonic small-volume resuscitation changed, currently indicating primary resuscitation from hypovolemia and shock by means of a hypertonic saline-colloid solution (Table 1).

The advantages of small-volume resuscitation

Based on experimental data obtained in cases of traumatic and hemorrhagic shock, it is possible to sum up the effects of primary resuscitation with hypertonic saline solution in isolation or in combination with hyperoncotic solutions as being[16]:

- Immediate increase in systemic pressure and cardiac output with reduced peripheral vascular resistance.
- Instantaneous increase in blood flow supply and reduced post-ischemic reperfusion lesions.
- Improvement in organic functions as observed by increased urinary output.
- Increased survival rates.

In addition, resuscitation with hypertonic solutions can reduce bacterial migration in rats subjected to hemorrhagic shock, a fact which is attributed to prevention of intestinal hypoperfusion.[17] It has been suggested that a hypertonic saline solution such as dextran is of benefit in improving microcirculatory disturbances post-burn and in attenuating mesenteric lipid peroxidation and systemic oxidization induced after burning.[18]

Pre-clinical use and efficacy

Current data from controlled clinical trials has shown that the use of small-volume resuscitation is practicable and effective compared with conventional fluid therapy for primary resuscitation of patients with trauma,[19] and also in the emergency room.[7] Research into the pre-hospital stage of resuscitation have demonstrated favorable results in cases of severe trauma requiring immediate surgery.[8] Data from a multicenter study[9] suggest that patients with trauma and hypotension, presenting a Glasgow coma score less than or equal to 8 may benefit from resuscitation with an NaCl solution at 7.5%. A revision performed by the Cochrane Library, however, revealed that there is a problem in terms of a lack of data proving the efficacy of hypertonic crystalloids in reducing mortality among patients with hypovolemia with or without head traumas.[10]

Table 1 - Definitions of terms used for small-volume resuscitation

Medical term	Definition
Small-volume resuscitation	Primary resuscitation from severe hypovolemia and shock by means of infusion in bolus of a small amount of a hypertonic solution (about 4ml/kg)
Hypertonic small-volume resuscitation (or hyperosmolar small-volume resuscitation)	Primary resuscitation from hemorrhages with a small amount of isolated hypertonic solution or combined with a colloid solution
Small-volume resuscitation via hypertonic-hyperoncotic solution	Primary resuscitation from hypotension due to hemorrhage by means of application of a bolus (in 2-5 minutes) of a small volume (saline solution combined with a hyperoncotic colloid solution [dextran 60/70 6-10%, hydroxyethyl starch 10%])
Small-volume resuscitation by means of hypertonic saline-colloid solution	Primary resuscitation from hypovolemia and shock by infusion in bolus (2-5 minutes) of a small volume of a hypertonic saline solution

A list of potential indications for small volume resuscitation in emergency care, during the perioperative period and in critically ill patients can be found in Table 2.

There are a number of different solutions available which contain hypertonic saline associated with a colloid agent (Table 3).

Some of the combined solutions (hypertonic NaCl/ colloid) are not available in our region, but in physiological terms the colloid adds specific beneficial effects, multiplying the effect of the hypertonic saline solution. However, the addition of a colloid compound can lead to an increased incidence of side effects, such as anaphylactic reaction.

Evidence from clinical trials

Researching thermal lesions, Horton et al.,[24,25] employing an experimental model using burnt pigs (45% of body surface area burnt), employed intravenous infusion with small volumes of saline at 7.5%/6% dextran-70 as a supplement to standard resuscitation with Ringer lactate. This strategy improved heart contraction performance, reduced cardiac myocyte damage and reduced total volume of fluids during the first 24 hours post burn. In 1973, Monafo et al.,[26] described the resuscitation of 25 children and 81 adults with a burnt area greater than 20%, using hypertonic saline solution at a number of different concentrations continuously. The data indicated that resuscitation volumes were 20 to 25% lower than those calculated by the Parkland formula. In 1983, Bowser et al.,[27] evaluated 39 children with large areas of burns resuscitated with hypertonic solution (17 patients), hypotonic solution (11 patients) or colloid (11 patients). Resuscitation with hypertonic solution resulted in lower sodium and water losses via the burn; produced a more significant increase in urinary volume than Ringer lactate infusion during the first 24 hours post burn; resulted in less weight gain; and had a better cost-effectiveness ratio than resuscitation with colloid solution. There were no statistically significant differences between the group on hypertonic solution and colloid solution, in respect of morbidity and mortality. These investigations concluded that hypertonic solutions are simple, safe and effective for acute burn management. More recently, Murph et al.[28] evaluated the systemic and resuscitation effects and also the safety of infusions of NaCl 7.5%/6% dextran-70 solution, given as a support during standard resuscitation with Ringer lactate after severe thermal damage, concluded that there were no adverse side effects related to hemodynamic or metabolic condition after infusion of the combined solution. Early administration of the combined solution after severe thermal lesion can reduce cardiac dysfunction related to burning.

Table 2 - Potential indications for small volume resuscitation in emergency care

Type of alteration/shock	Phase	Impact
Trauma	Prehospital	Substitution of volume, microvascular resuscitation
	Emergency room	Microcirculatory resuscitation
	Perioperative	Substitution of volume
Head trauma	Increase in intracranianal pressure	Reduction in intracranial pressure, better cerebral blood flow
Hypovolemic shock	Anaphylaxis	Increase in volume
	Perioperative	Substitution of volume (in cases of sudden bleeding)
Septic shock	Hyperdinamic	Substitution of volume, microcirculatory resuscitation, increase in tissue oxygen
	Hypodinamic	Reopening of collapsed capillaries, microcirculatory resuscitation
Burning	Initial phase	Reduction in edema occurence, microcirculatory resuscitation, reduction in bacterial translocation
Intensive care	Multiorgan failure, organic failure	Better blood flow and improvement of organs function, reduction in bacterial translocation
Cardiogenic shock	Stroke	Replacement of volume without overload risk, positive inotropic effect
Cardiovascular surgery	Surgery	Reduction in the necessity of volume, reduction in volume allowed in a less positive fluid balance
Anesthesiology management	Epidural anesthesia	Generally not indicated since there are other good alternatives
	Physiological replacement of volume	Generally not indicated

Table 3 - Characteristics of products of hypertonic solutions used in the clinic practice

Product	Main substance	Content/ recipient	Osmolarity (mOsmol/l)	Content of sodium with the infusion of 250 ml of volume
Solution of NaCl 0.9%	Sodium chloride 9g/l	500 ml	309	39 mmol
Glucose 20%	Glucose 200g/l	500 ml	1,110	None
Glucose 40%	Glucose 400g/l	500 ml	2,220	None
RescueFlow	NaCl 7.5%/ dextran 70 6%	250 ml	2,567	321 mmol
HyperHAES	NaCl 7.2%/ hydroxyethyl starch 6%	250 ml	2,264	308 mm

The use of hyperosmotic solutions during heart surgery was first carried out by Boldt et al.[29] who demonstrated that there were significantly lower volume requirements when a hypertonic saline solution was used in comparison with a standard solution of hydroxyethyl starch to correct hypovolemia observed after extracorporeal circulation. In order to double the level of pulmonary capillary pressure, just 3.1 ml/kg of hypertonic saline solution were necessary compared with a volume of 10.3 ml/kg of hydroxyethyl starch at 6%. Later, Oliveira et al.[30] used hypertonic-hyperoncotic solution to double pulmonary capillary pressure before extracorporeal circulation in patients who were Jehovah's witnesses, finding that all patients maintained a stable metabolic and hemodynamic condition with increased cardiac output, lower vascular resistance and a mildly negative fluid balance. None of the patients needed blood transfusions. Tollofsrud et al.[31] infused hypertonic-hyperoncotic solutions in 10 patients post extracorporeal circulation and reported a reduction in fluids required to stabilize hemodynamic status and a significantly increased cardiac index, elevated urinary output and a post-op fluid balance that was significantly lower. Indicators of pulmonary function were different between the control group and the group that received hypertonic-hyperoncotic solution, suggesting that the excess interstitial fluid may be mobilized by the combined solution, thus contributing to reduced edema formation and improved tissue perfusion.

A new application for hypertonic saline solution which is currently emerging is its use for advanced cardiac failure, Licata et al.[32] administered 150 ml of hypertonic saline solution to 53 patients with advanced refractory heart failure associated with a high dose of intravenous furosemide (500-1,000 mg twice a day) and compared them with 54 patients who received the same dose of furosemide without the hypertonic solution supplementation. The patients who received hypertonic solution had a better hospital course than those who did not receive it. These patients had shorter hospital stays, less renal dysfunction, better sodium levels on discharge and fewer adverse effects from the use of furosemide. An editorial, by Tex D, 2003,[33] makes the comment that double-blind, randomized clinical trials are necessary to better define the role of hypertonic solutions as treatment for patients with advanced refractory cardiac failure.

In 1997, Wade et al.[34] performed a meta-analysis of research in which hypertonic saline solution/dextran or hypertonic saline solution in isolation had been used as the primary fluid therapy for patients with traumatic lesions. The analysis included eight studies evaluating a total of 1,170 patients. The inclusion criterion for trauma patients was systolic arterial pressure below 100 mmHg. There were no significant differences in 30-day survival rates when hypertonic saline solution (7.5%) was compared with Ringer lactate, however, there was a 5.1% increase in survival rates when hypertonic saline solution/dextran (NaCl 7.5%/6% dextran-70) was compared.

When the role of hypertonic solutions in septic shock was analyzed, animal research,[35] demonstrated a significant reduction in albumin leakage, in neutrophil counts from broncho-alveolar lavage and in the degree of histopathological damage when compared with resuscitation with Ringer lactate. There are few studies of humans which have evaluated hypertonic solution in patients with sepsis. One of these demonstrates improvements in resuscitation parameters among clinically stable sepsis patients.[36] Twenty-none patients were included in the study and received either

250 ml saline or hypertonic solution (NaCl 7.5%/8% dextran-70). Cardiac index and systolic volume were greater in the group that received hypertonic solution, with differences being most apparent 1 hour after infusion.

Currently there is interest in the use of hypertonic solutions as osmotic substances which increase intravascular volume and combat increased intracranial pressure.[37,38] In humans hypertonic saline solutions reduce intracranial pressure, increase intravascular volume and improve resuscitation performance.[21,39] Research carried out by Fisher et al.,[40] a randomized, controlled trial, observed reduced intracranial pressure in 18 children with traumatic brain damage, for a period of two hours when hypertonic saline solution was compared with a same-volume dose of saline. Shimma et al.[41] compared the effects of Ringer lactate and hypertonic saline on children with severe head trauma during the first three days of the trauma, concluding that serum sodium increases had a significant correlation with reduced intracranial pressure and increased cerebral perfusion pressure. Hypertonic saline solution has also been used with other conditions associated with increased intracranial pressure, as in work by Suarez et al.,[42] who evaluated the effects of administering 23.4% saline intravenously for refractory hypertension intracranial with eight patients with a number of different intracranial conditions, concluding that hypertonic solution reduces intracranial pressure and significantly improves cerebral perfusion pressure. Another study by the same group of authors,[38] describes the evolution of cerebral edema and intracranial pressure in a heterogeneous group of critically ill patients who were treated with a hypertonic solution of NaCl/acetate 3%. The infusion was maintained at a velocity of 75-150ml/hour until the patients demonstrated clinical improvement, developed complications or there was a failure to respond after sodium levels had reached 135-155 mmol/L. Reductions were also observed in average intracranial pressure during the first 12 hours among head trauma patients and those with edema in post-op, but the same effect was not observed among the patients with non-traumatic intracranial hemorrhage or cerebral infarction.

A small retrospective study performed by Peterson et al.[43] evaluated 68 children with head trauma with whom hypertonic solution of NaCl at 3% was used with the objective of reducing intracranial pressure to $\leq$ 20 mmHg. The treatment effectively reduced intracranial pressure in these patients, and only three deaths were observed (4%) due to uncontrolled intracranial pressure. The graph for one patient, analyzed in isolation, is presented in Figure 4.

Another prospective study, by Kanna et al.,[44] evaluated the effect of prolonged infusion of NaCl solution at 3% with 10 pediatric patients with traumatic brain damage and refractory hypertension intracranial despite conventional treatments.

Hypertonic solution of NaCl works by increasing sodium and serum osmolality, creating an osmotic gradient which transfers water from the intracellular compartment of the brain to the interstitial, thus reducing cerebral edema and intracranial pressure. While mannitol has a similar action, sodium chloride has a more favorable reflection coefficient (1.0) than does mannitol (0.9), making hypertonic solutions ideal agents when these effects are desired. Hypertonic solution can also normalize the resting membrane potential and cell volume, restoring the intracellular electrolyte balance of damaged cells, suggesting that this treatment could have preferential benefits in damaged areas of the brain.[45]

Disadvantages and potential adverse effects

The infusion in bolus of a hypertonic NaCl solution to a peripheral vein at a concentration above 10% causes significant hemolysis while solutions at 7-7.5% are reported to be safe. Although the concept of resuscitation with hypertonic solutions involves a considerable increase in osmolar charge, work carried out to date does not report any acute clinical signs of hyperosmolality. Serum osmolality reduces after the first 4-8 hours of infusion and, after 24 hours there is no difference between patients who have received hypertonic saline solution and controls.[20,46]

There may also be electrolyte disturbances, primarily related to the sodium. Neuropathological signs of continuous central myelinolysis were not found in any of the patients that died. Chlorine levels also increase and may be associated with acidosis (hyperchloremic acidosis).

The addition of a crystalloid solution is also not immune to risks, primarily anaphylactic reactions. However, none of the controlled clinical trials attributed adverse effects to the colloid component.[34]

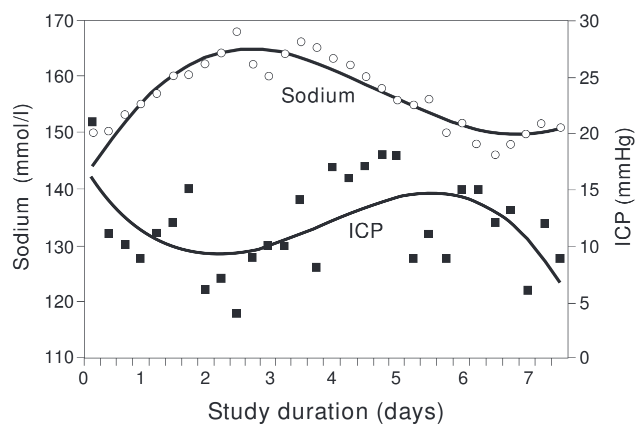

Figure 4 - Serum sodium and intracranial pressure curves according to time in a patient. Note the inverse relation between serum sodium and intracranial pressure, which was statistically significant in all patients ($p < 0.05$)

Potential side effects associated with small-volume resuscitation are shown in Table 4.

Table 4 - Potential side effects associated with small-volume resuscitation

Hyperosmolar coma
Hypernatremia
Hypopotassemia
Seizures
Arrhythmia
Negative inotropic effect (after rapid infusion)
Tissue necrosis (in cases of extravasation)
Hemoyisis (in the puncture site)
Increase in bleeding (in non-controlled hemorrhage)
Anaphylaxis (related to colloid component)

Other effects of hypertonic solutions

Some physiological alterations associated with hypertonic fluids include alterations to the cytotoxicity of leukocytes,[47] pulmonary of neutrophils sequestration,[35] neutrophils activation[48] and alterations to vascular permeability induced by endotoxins.[49]

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